PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 May 1999 (05.05.99)	
International application No. PCT/AU98/00724	**Applicant's or agent's file reference** 2093266/JMS
International filing date (day/month/year) 04 September 1998 (04.09.98)	**Priority date** (day/month/year) 08 September 1997 (08.09.97)
Applicant NG, Frank, Man-Woon et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

01 April 1999 (01.04.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2093266/JMS :ETC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. **PCT/AU 98/00724**	International filing date *(day/month/year)* 4 September 1998	Priority Date *(day/month/year)* 8 September 1997
International Patent Classification (IPC) or national classification and IPC **Int. Cl.**[6] C07K 14/61, 7/08, A61K 38/27		
Applicant Metabolic Pharmaceuticals Ltd (et al.)		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

Date of submission of the demand 1 April 1999	Date of completion of the report 30 August 1999
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. (02) 6285 3929	Authorised Officer **G. D. HEARDER** Telephone No. (02) 6283 2553

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU 98/00724

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1, 2, 4-43, 44-46,** as originally filed,
pages , filed with the demand,
pages , filed with the letter of
pages **3,** filed with the letter of **10 August 1999**

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **47-52,** filed with the letter of **5 July 1999.**

☒ the drawings, pages **1/21-21/21,** as originally filed,
pages , filed with the demand,
pages , filed with the letter of .

☒ the sequence listing part of the description:
pages **1-13,** as originally filed
pages , filed with the demand
pages , filed with the letter of .

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages

☒ the claims, Nos. **2-6, 19-33**

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-36	YES
	Claims		NO
Inventive step (IS)	Claims	1-36	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-36	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Claims 1-36

The invention of the amended claims is directed to peptides which are specific analogues of the carboxyl-terminal sequence of human growth hormone or a corresponding sequence of a non-human mammalian growth hormone.

No individual citation or obvious combination of citations disclose the features of these claims.

The closest art of:

AU 77727/94

Discloses hGH 177-191 and analogues thereof, but it does not disclose or teach the specific peptides of the amended claims.

invention has been directed to investigating whether hGH derivatives could be synthesised that retain the desired bioactivities and lack the unwanted side effects.

The structure-function studies of hGH with synthetic hormonal fragments have revealed that the carboxyl terminus of the hGH molecule appears to be the functional domain of the hormone for the regulation of lipid metabolism[20,23] and it has been shown that a synthetic peptide having a sequence based in the carboxyl terminal region reduces body weight gain and adipose tissue mass in a laboratory obese animal model.

The entire contents of US Patent No. 5869452, issued on Application Serial No. 08/340389, dated 15 November 1994, including the specification, claims and figures, are incorporated herein by reference in their entirety.

SUMMARY OF THE INVENTION

The present invention provides a peptide which comprises an analogue of the carboxyl-terminal sequence of a growth hormone. The peptide may comprise an analogue of the carboxyl-terminal sequence of human growth hormone or the growth hormone of a non-human mammalian species. As described above, the carboxyl-terminal sequence of growth hormone includes a bioactive lipid metabolic domain. In one embodiment of the invention, the peptide comprises an analogue of the carboxyl-terminal sequence of human growth hormone containing amino acid residues 177-191 or a corresponding sequence of a non-human mammalian growth hormone. The analogue may be obtained by insertion, deletion or substitution of amino acids in, or chemical modification of, the native carboxyl-terminal sequence of human growth hormone or the growth hormone of a non-human mammalian species.

CLAIMS:

1. (Amended) A peptide which comprises an analogue of the carboxyl-terminal sequence of a growth hormone, said carboxyl-terminal sequence containing amino acid residues 177-191 of human growth hormone:
Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe,
or a corresponding sequence of a non-human mammalian growth hormone; wherein in said analogue

(i) amino acids at positions 182 and 189 of hGH are joined by a bond to promote a cyclic conformation; and/or

(ii) amino acids at positions 183 and 186 of hGH are joined by a salt bridge or a covalent bond;

or an organic or inorganic acid addition salt thereof.

2. (Cancelled).

3. (Cancelled).

4. (Cancelled).

5. (Cancelled).

6. (Cancelled).

7. (Amended) A peptide according to claim 1, wherein the bond between amino acids at positions 182 and 189 is a disulfide bond.

8. (Amended) A peptide according to claim 1, wherein the amino acids at positions182 and 189 are selected from the group consisting of L-Cys, D-Cys, L-Pen and D-Pen.

9. (Amended) A peptide according to claim 16, wherein the amino acids at positions 183 and 186 are joined by a salt bridge, and are (X and Y) or (Y and X), respectively, where:

X is a positively charged amino acid, and

Y is a negatively charged amino acid.

10. A peptide according to claim 9, wherein X is selected from the group consisting of L- or D-Arg, Lys and Orn, and Y is selected from the group consisting of L- or D-Asp and Glu.

11. (Amended) A peptide according to claim 1, wherein the amino acids at positions 183 and 186 are joined by an amide covalent bond.

12. (Amended) A peptide according to claim 11, wherein the amino acids at positions 183 and 186 are (X and Y) or (Y and X), respectively, where:

X is selected from the group consisting of L- or D- Lys and Orn, and

Y is selected from the group consisting of L- or D- Asp and Glu.

13. (Amended) A peptide of the sequence:

X^1m-Leu-Arg-Ile-Val-Gln-Cys-Arg -Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-X^2n

wherein X^1 and X^2 are each selected from the group consisting of L- or D- Arg, His, Lys and Tyr, and m and n are each 0, 1, 2 or 3 with the proviso that at least m or n is 1;

a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

14. (Amended) A peptide of the sequence:

Y^1-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe

wherein Y^1 is selected from the group consisting of the desamino form (H), acetyl (CH_3CO-) and other acyl groups;

a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

15. (Amended) A peptide of the sequence:

Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-Y^2

wherein Y^2 is selected from the group of $CONH_2$ and alkyl amide groups;

a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

16. (Amended) A peptide which is selected from the group consisting of:

Ref No.	STRUCTURE
9502	Leu Arg Ile Val Gln Pen Arg Ser Val Glu Gly Ser Pen Gly Phe
9405	CH_3CO- Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9410	H - Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9404	Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe - $CONH_2$
9407	Leu Arg Ile Val Gln Cys Lys Ser Val Glu Gly Ser Cys Gly Phe
9408	Leu Arg Ile Val Gln Cys Lys Ser Val Glu Gly Ser Cys Gly Phe |_____|(amide bond)
9604	Tyr Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9605	Lys Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9618	Lys Lys Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9607	Ala Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9606	Leu Lys Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9608	Leu Arg Ala Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9403	Leu Arg Lys Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9609	Leu Arg Ile Ala Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9610	Leu Arg Ile Val Ala Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9612	Leu Arg Ile Val Gln Cys Arg Ala Val Glu Gly Ser Cys Gly Phe
9613	Leu Arg Ile Val Gln Cys Arg Ser Ala Glu Gly Ser Cys Gly Phe
9615	Leu Arg Ile Val Gln Cys Arg Ser Val Glu Ala Ser Cys Gly Phe
9616	Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ala Cys Gly Phe
9602	Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Ala Phe
9501	Leu Arg Ile Val Gln Cys Arg Ser Val Glu D-Ala Ser Cys D-Ala Phe
9601	Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Ala

wherein the amino acid residue abbreviations used are in accordance with the standard peptide nomenclature:

Gly	=	Glycine;	Ile	=	Isoleucine;
Glu	=	Glutamic Acid;	Phe	=	Phenylalanine;
Cys	=	Cysteine;	Arg	=	Arginine;
Gln	=	Glutamine;	Leu	=	Leucine;
Ser	=	Serine;	Val	=	Valine;
Lys	=	Lysine;	Ala	=	Alanine;
Asp	=	Aspartic acid;	His	=	Histidine;

Orn = Ornithine; Tyr = Tyrosine;

Pen = Penicillamine (β,β'-Dimethyl-Cysteine).

wherein all amino acids, except for glycine, are of the L-absolute configuration, unless indicated as D-absolute configuration, and the peptide has a cyclic disulfide bond between Cys(182) and Cys(189) or Pen(182) and Pen(189) as appropriate,

or an organic or inorganic acid addition salt thereof.

17. (Amended) A method for the treatment of obesity in an animal, which comprises administering to the animal an effective amount of a peptide according to any one of claims 1 or 7 to 16.

18. A method according to claim 17, wherein the animal is a human.

19. (Cancelled).

20. (Cancelled).

21. (Cancelled).

22. (Cancelled).

23. (Cancelled).

24. (Cancelled).

25. (Cancelled).

26. (Cancelled).

27. (Cancelled).

28. (Cancelled).

29. (Cancelled).

30. (Cancelled).

31. (Cancelled).

32. (Cancelled).

33. (Cancelled).

34. (Amended) A method according to claim 17 or claim 18, wherein the peptide is administered orally.

35. (Amended) Use of a peptide according to any one of claims 1 or 7 to 16 in the manufacture of a pharmaceutical composition for the treatment of obesity in an animal.

36. (Amended) A pharmaceutical composition for use in the treatment of obesity in an animal, which comprises an effective amount of a peptide according to any one of claims 1 to 7 or 16, together with one or more pharmaceutically acceptable carriers and/or diluents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00724

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C07K 14/61, 7/08, A61K 38/27

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN protein subsequence search [AlaLeu]-[LysArg]-[LysAlaIle]-[ValAla]-[GlnAla]-[CysPen]-[LysArg]-[SerAla]-[ValAla]-Glu-[GlyAla]-[SerAla]-[CysPen]-[GlyAla]-[PheAla]/sqsp SQL ≤20

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU, B 77727/94 (693478) (MONASH UNIVERSITY) 16 May 1996 entire document, see especially pages 3-5.	1-36
X	Biochemistry and Molecular Biology International, vol. 33 no. 5, 1994, F. M. Ng et al. "Reduction of cumulative body weight gain and adipose tissue mass in obese mice..." pages 1011-1021. entire document	1-36
X	Biochemistry and Molecular Biology International, vol. 30 no. 1, 1993, F. M. Ng et al, "Antilipogenic action of synthetic C-terminal sequence 177-191 of human growth hormone" pages 187-196. entire document	1-36

[X] Further documents are listed in the continuation of Box C

[ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 1998	19 OCT 1998
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer IAN DOWD Telephone No.: (02) 6283 2273

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00724

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Acta Endocrinologica, vol. 101, 1982, J. D. Wade et al., "Effect of C-terminal chain shortening on the insulin-antagonistic activity of human growth hormone 177-191", pages 10-14.	
X	entire document	1-16
Y		17-36
	Biochimica et Biophysica Acta, vol. 716, 1982, G. Y. W. Ma et al., "The mechanism of the hyperglycaemic action of synthetic peptides related to the C-terminal sequence of human growth hormone", pages 400-409.	
X	entire document	1-16
Y		17-36
	International Journal of Peptide and Protein Research, vol. 13(2), 1979, J. D. Wade et al., "Diabetogenic action of human growth hormone", pages 195-200.	
X	entire document	1-16
Y		17-36
	American Journal of Physiology, vol. 236, 1979, C. Weerasinghe et al., "Effect of synthetic C-terminal fragments of hGH on glucose oxidation by isolated islets", pages E4-E9.	
X	entire document	1-16
Y		17-36
	Biochimica et Biophysica Acta, vol. 544, 1978, J. D. Newman et al., "Effects of part sequences of human growth hormone on in vivo hepatic glycogen metabolism in the rat", pages 234-244.	
X	entire document	1-16
Y		17-36
	Trends in Biochemical Sciences, vol. 3, 1978, J. Bornstein, "Biological actions of synthetic part seqences of human growth hormone", pages 83-86.	
X	entire document	1-16
Y		17-36
	Growth Hormone and Related Peptides: Proceedings of the IIIrd International Symposium, Milan, September 17-20, 1975, J. Bornstein, "In vivo and in vitro actions of synthetic part sequences of human pituitary growth hormone", pages 41-49.	
X	entire document	1-16
Y		17-36
	Hormone Research, vol. 38, 1992, J. M. Gertner, "Growth hormone actions on fat distribution and metabolism", pages 41-43.	
Y	entire document	17-36

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00724

Box 1 Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: **17-34**
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17 to 34 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds

2. [X] Claims Nos.: **1-3(in part)**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

These claims were deemed unsearchable for economic reasons. The search has been limited to what has been exemplified.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07K 14/61, 7/08, A61K 38/27

A1

(11) International Publication Number: WO 99/12969

(43) International Publication Date: 18 March 1999 (18.03.99)

(21) International Application Number: PCT/AU98/00724

(22) International Filing Date: 4 September 1998 (04.09.98)

(30) Priority Data:

PO 9001	8 September 1997 (08.09.97)	AU
PP 0398	13 November 1997 (13.11.97)	AU

(71) Applicant *(for all designated States except US)*: METABOLIC PHARMACEUTICALS LTD. [AU/AU]; 10 Wallace Avenue, Toorak, VIC 3142 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: NG, Frank, Man-Woon [AU/AU]; 144 Edgevale Road, Kew, VIC 3101 (AU). JIANG, Woei-Jia [-/AU]; Flat 7, 86 Wellington Road, Clayton, VIC 3168 (AU).

(74) Agents: SLATTERY, John, M. et al.; Davies Collison Cave, 1 Little Collins Street, Melbourne, VIC 3000 (AU).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: TREATMENT OF OBESITY

(57) Abstract

A method for the treatment of obesity in an animal such as a human, comprises administering to the animal an effective amount of a peptide which comprises an analogue of the carboxyl-terminal sequence of a growth hormone, particularly an analogue of the carboxyl-terminal sequence of human growth hormone containing amino acid residues 177-191. A pharmaceutical composition for use in the treatment of obesity is also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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EE	Estonia	**LR**	Liberia	**SG**	Singapore		

invention has been directed to investigating whether hGH derivatives could be synthesised that retain the desired bioactivities and lack the unwanted side effects.

The structure-function studies of hGH with synthetic hormonal fragments have revealed that the carboxyl terminus of the hGH molecule appears to be the functional domain of the hormone for the regulation of lipid metabolism[20,23] and it has been shown that a synthetic peptide having a sequence based in the carboxyl terminal region reduces body weight gain and adipose tissue mass in a laboratory obese animal model.

The entire contents of US Patent Application Serial No. 08/340389, dated 15 November 1994, including the specification, claims and figures, are incorporated herein by reference in their entirety.

SUMMARY OF THE INVENTION

The present invention provides a peptide which comprises an analogue of the carboxyl-terminal sequence of a growth hormone. The peptide may comprise an analogue of the carboxyl-terminal sequence of human growth hormone or the growth hormone of a non-human mammalian species. As described above, the carboxyl-terminal sequence of growth hormone includes a bioactive lipid metabolic domain. In one embodiment of the invention, the peptide comprises an analogue of the carboxyl-terminal sequence of human growth hormone containing amino acid residues 177-191 or a corresponding sequence of a non-human mammalian growth hormone. The analogue may be obtained by insertion, deletion or substitution of amino acids in, or chemical modification of, the native carboxyl-terminal sequence of human growth hormone or the growth hormone of a non-human mammalian species.

CLAIMS:

1. A peptide which comprises an analogue of the carboxyl-terminal sequence of a growth hormone.

2. A peptide according to claim 1, which comprises an analogue of the carboxyl-terminal sequence of human growth hormone.

3. A peptide according to claim 1, which comprises an analogue of the carboxyl-terminal sequence of a non-human mammalian growth hormone.

4. A peptide according to claim 1, which comprises an analogue of the carboxyl-terminal sequence of human growth hormone containing amino acid residues 177-191,
Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe,
or a corresponding sequence of a non-human mammalian growth hormone,
a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

5. A peptide according to claim 1, which is obtained by elongation, insertion, deletion or substitution of amino acids in, or chemical modification of, or introduction of a cyclic amide bond between the side chains of amino acids of the native carboxyl-terminal sequence of human growth hormone containing amino acid residues 177-191, a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

6. A peptide according to claim 5, wherein

(i) amino acids at positions 182 and 189 of hGH are joined by a bond to promote a cyclic conformation; and/or

(ii) amino acids at positions 183 and 186 of hGH are joined by a salt bridge or a covalent bond.

7. A peptide according to claim 6, wherein the bond between amino acids at positions 182 and 189 of hGH is a disulfide bond.

8. A peptide according to claim 6, wherein the amino acids at positions182 and 189 of hGH are selected from the group consisting of L-Cys, D-Cys, L-Pen and D-Pen.

9. A peptide according to claim 6, wherein the amino acids at positions 183 and 186 of hGH are joined by a salt bridge, and are (X and Y) or (Y and X), respectively, where:

X is a positively charged amino acid, and

Y is a negatively charged amino acid.

10. A peptide according to claim 9, wherein X is selected from the group consisting of L- or D-Arg, Lys and Orn, and Y is selected from the group consisting of L- or D-Asp and Glu.

11. A peptide according to claim 6, wherein the amino acids at positions 183 and 186 of hGH are joined by an amide covalent bond.

12. A peptide according to claim 11, wherein the amino acids at positions 183 and 186 of hGH are (X and Y) or (Y and X), respectively, where:

X is selected from the group consisting of L- or D- Lys and Orn, and

Y is selected from the group consisting of L- or D- Asp and Glu

13. A peptide according to claim 5, of the sequence:

X^1m-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-X n wherein X^1 and X^2 are each selected from the group consisting of L- or D- Arg, His, Lys and Tyr, and m and n are each 0, 1, 2 or 3 with the proviso that at least m or n is 1, a cyclic disulfide thereof or an organic or inorganic and addition salt thereof.

14. A peptide according to claim 5, of the sequence:
Y^1-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe
wherein Y^1 is selected from the group consisting of the desamino form (H), acetyl (CH_3CO-) and other acyl groups;
a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

15. A peptide according to claim 5, of the sequence:
Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-Y^2
wherein Y^2 is selected from the group of $CONH_2$ and alkyl amide groups,
a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

16. A peptide according to claim 5, which is selected from:

Ref No.	STRUCTURE
9502	Leu Arg Ile Val Gln Pen Arg Ser Val Glu Gly Ser Pen Gly Phe
9405	CH_3CO- Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9410 H - Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9404 Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe - $CONH_2$

9407 Leu Arg Ile Val Gln Cys Lys Ser Val Glu Gly Ser Cys Gly Phe

9408 Leu Arg Ile Val Gln Cys Lys Ser Val Glu Gly Ser Cys Gly Phe
|_____|(amide bond)

9604 Tyr Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9605 Lys Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9618 Lys Lys Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9607 Ala Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9606 Leu Lys Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9608 Leu Arg Ala Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9403 Leu Arg Lys Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9609 Leu Arg Ile Ala Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9610 Leu Arg Ile Val Ala Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9612 Leu Arg Ile Val Gln Cys Arg Ala Val Glu Gly Ser Cys Gly Phe

9613 Leu Arg Ile Val Gln Cys Arg Ser Ala Glu Gly Ser Cys Gly Phe

9615 Leu Arg Ile Val Gln Cys Arg Ser Val Glu Ala Ser Cys Gly Phe

9616 Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ala Cys Gly Phe

9602 Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Ala Phe

9501 Leu Arg Ile Val Gln Cys Arg Ser Val Glu D-Ala Ser Cys D-Ala Phe

9601 Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Ala

wherein the amino acid residue abbreviations used are in accordance with the standard peptide nomenclature:

Gly	=	Glycine;	Ile	=	Isoleucine;
Glu	=	Glutamic Acid;	Phe	=	Phenylalanine;
Cys	=	Cysteine;	Arg	=	Arginine;
Gln	=	Glutamine;	Leu	=	Leucine;
Ser	=	Serine;	Val	=	Valine;
Lys	=	Lysine;	Ala	=	Alanine;
Asp	=	Aspartic acid;	His	=	Histidine;
Orn	=	Ornithine;	Tyr	=	Tyrosine;
Pen	=	Penicillamine (β,β'-Dimethyl-Cysteine).			

wherein all amino acids, except for glycine, are of the L-absolute configuration, unless indicated as D-absolute configuration, and the peptide has a cyclic disulfide bond between Cys(182) and Cys(189) or Pen(182) and Pen(189) as appropriate,

or an organic or inorganic acid addition salt thereof.

17. A method for the treatment of obesity in an animal, which comprises administering to the animal an effective amount of a peptide which comprises an analogue of the carboxyl-terminal sequence of a growth hormone.

18. A method according to claim 17, wherein the animal is a human.

19. A method according to claim 17 or claim 18, wherein the peptide comprises an analogue of the carboxyl-terminal sequence of human growth hormone.

20. A method according to claim 17 or claim 18, wherein the peptide comprises an analogue of the carboxyl-terminal sequence of a non-human mammalian growth hormone.

21. A method according to claim 17 or claim 18, wherein the peptide comprises an analogue of the carboxyl-terminal sequence of human growth hormone containing amino acid residues 177-191,
Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe,
or a corresponding sequence of a non-human mammalian growth hormone,
a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

22. A method according to claim 17 or claim 18, wherein the analogue is obtained by elongation, insertion, deletion or substitution of amino acids in, or introduction of a cyclic amide bond between the side chains of amino acids of, or chemical modification of, the native carboxyl-terminal sequence of human growth hormone containing amino acid residues 177-191, a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

23. A method according to claim 22, wherein the analogue comprises a peptide wherein:

(i) amino acids at positions 182 and 189 of hGH are joined by a bond to promote a cyclic conformation; and/or

(ii) amino acids at positions 183 and 186 of hGH are joined by a salt bridge or a covalent bond.

24. A method according to claim 23, wherein the bond between amino acids at positions 182 and 189 of hGH is a disulfide bond.

25. A method according to claim 23, wherein the amino acids at positions182 and 189 of hGH are selected from the group consisting of L-Cys, D-Cys, L-Pen and D-Pen.

26. A method according to claim 23, wherein the amino acids at positions 183 and 186 of hGH are joined by a salt bridge, and are (X and Y) or (Y and X), respectively, where:

X is a positively charged amino acid, and

Y is a negatively charged amino acid.

27. A method according to claim 26, wherein X is selected from the group consisting of L- or D-Arg, Lys and Orn, and Y is selected from the group consisting of L- or D-Asp and Glu.

28. A method according to claim 23, wherein the amino acids at positions 183 and 186 of hGH are joined by an amide covalent bond.

29. A method according to claim 28, wherein the amino acids at positions 183 and 186 of hGH are (X and Y) or (Y and X), respectively, where:

X is selected from the group consisting of L- or D- Lys and Orn and

Y is selected from the group consisting of L- or D- Asp and Glu

30. A method according to claim 22, wherein the analogue comprises a peptide of the sequence:

X^1m-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-X^2 n

wherein X^1 and X^2 are each selected from the group consisting of L- or D- Arg, His, Lys and Tyr and m and n are each 0, 1, 2 or 3 with the proviso that at least m or n is 1,

a cyclic disulfide thereof or an organic and inorganic acid addition salt thereof.

31. A method according to claim 22, wherein the analogue comprises a peptide of the sequence:

Y^1-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe

wherein Y^1 is selected from the group consisting of the desamino form (H), acetyl (CH_3CO-) and other acyl groups,

a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

32. A method according to claim 22, wherein the analogue comprises a peptide of the sequence:

Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-Y^2

wherein Y^2 is selected from the group of $CONH_2$ and alkyl amide groups,

a cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

33. A method according to claim 20, wherein the analogue comprises a peptide selected from:

Ref No.	STRUCTURE
9502	Leu Arg Ile Val Gln Pen Arg Ser Val Glu Gly Ser Pen Gly Phe
9405	CH_3CO- Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9410	H - Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9404	Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe - $CONH_2$
9407	Leu Arg Ile Val Gln Cys Lys Ser Val Glu Gly Ser Cys Gly Phe
9408	Leu Arg Ile Val Gln Cys Lys Ser Val Glu Gly Ser Cys Gly Phe |_____|(amide bond)
9604	Tyr Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe

9605	Lys Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9618	Lys Lys Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9607	Ala Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9606	Leu Lys Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9608	Leu Arg Ala Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9403	Leu Arg Lys Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9609	Leu Arg Ile Ala Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9610	Leu Arg Ile Val Ala Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
9612	Leu Arg Ile Val Gln Cys Arg Ala Val Glu Gly Ser Cys Gly Phe
9613	Leu Arg Ile Val Gln Cys Arg Ser Ala Glu Gly Ser Cys Gly Phe
9615	Leu Arg Ile Val Gln Cys Arg Ser Val Glu Ala Ser Cys Gly Phe
9616	Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ala Cys Gly Phe
9602	Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Ala Phe
9501	Leu Arg Ile Val Gln Cys Arg Ser Val Glu D-Ala Ser Cys D-Ala Phe
9601	Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Ala

wherein the amino acid residue abbreviations used are in accordance with the standard peptide nomenclature:

Gly	=	Glycine;	Ile	=	Isoleucine;
Glu	=	Glutamic Acid;	Phe	=	Phenylalanine;
Cys	=	Cysteine;	Arg	=	Arginine;
Gln	=	Glutamine;	Leu	=	Leucine;
Ser	=	Serine;	Val	=	Valine;
Lys	=	Lysine;	Ala	=	Alanine;
Asp	=	Aspartic acid;	His	=	Histidine;

Orn = Ornithine; Tyr = Tyrosine;
Pen = Penicillamine (β,β'-Dimethyl-Cysteine).

wherein all amino acids, except for glycine, are of the L-absolute configuration, unless indicated as D-absolute configuration, and the peptide has a cyclic disulfide bond between Cys(182) and Cys(189) or Pen(182) and Pen(189) as appropriate,

or an organic or inorganic acid addition salt thereof.

34. A method according to any of claims 17 to 33, wherein the peptide is administered orally.

35. Use of a peptide according to any of claims 1 to 16 in the manufacture of a pharmaceutical composition for the treatment of obesity in an animal.

36. A pharmaceutical composition for use in the treatment of obesity in an animal, which comprises an effective amount of a peptide according to any one of claims 1 to 16, together with one or more pharmaceutically acceptable carriers and/or diluents.